Environmental Health Perspectives
Vol. 25, pp. 129-132, 1978

Cadmium and Zinc Relationships

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Cadmium and zinc concentrations in kidney and liver have been measured under different exposure situations in different species including man. The results show that zinc increases almost equimolarly with cadmium in kidney after long-term low-level exposure to cadmium, e.g., in man, horse, pig, and lamb. In contrast, the increase of zinc follows that of cadmium to only a limited extent, e.g., in guinea pig, rabbit, rat, mouse, and chicks.

In liver, the cadmium–zinc relationship seems to be reversed in such a way that zinc increases with cadmium more markedly in laboratory animals than in higher mammals. These differences between cadmium and zinc relationships in humans and large farm animals and those in commonly used laboratory animals must be considered carefully before experimental data on cadmium and zinc relationships in laboratory animals can be extrapolated to humans.

Cadmium and Zinc Interactions

Cadmium is a nonessential metal which accumulates in the mammalian body, especially in kidney and liver. A concentration of cadmium in kidney cortex exceeding 200 μg/g wet weight may give rise to tubular proteinuria (*1*).

Zinc, which has several physicochemical similarities to cadmium, is, in contrast to cadmium, essential and counteracts a number of the toxic effects of cadmium. Parizek (*2*) and Gunn et al. (*3*) demonstrated that simultaneous subcutaneous administration of zinc and cadmium to rats protected against the severe testicular injury observed when cadmium was given alone. Gunn et al. (*4*) reported also that cadmium-induced testis tumors were prevented by administration of zinc. Schroeder and Buckman (*5*) showed that the increased blood pressure in rats given cadmium could be reduced by injection of zinc chelate. A marginal zinc intake by rats gives rise to higher cadmium absorption and retention compared to animals given excess of zinc (*6*). Furthermore, a low peroral intake of cadmium aggravated the symptoms of zinc deficiency in rats (*7*).

In a number of *in vitro* studies, cadmium has been shown to decrease the activities of zinc-dependent enzymes (*8*, *9*). It has been proposed that the toxicity of cadmium, at least partly, can be explained by a competition between cadmium and zinc at cofactor sites in enzymes requiring zinc, resulting in decreased activities of these enzymes (*9*). Thus, the tubular proteinuria which occurs at high renal cadmium concentrations might be explained by decreased activities of certain zinc requiring enzymes, such as alkaline phosphatase and leucineaminopeptidase, which both are located in the brush border of the proximal tubules, and are speculated to be engaged in the tubular reabsorption of proteins (*10*). Reduced activities of these enzymes in kidney has been observed in pigs and rats perorally exposed to cadmium (*11*, *12*).

Cadmium and Zinc Relationships

In higher mammals, such as man, horse, and pig, zinc concentrations in renal cortex have been shown to increase on an equimolar basis with the increase of cadmium up to a cadmium level of about 50 to 70 μg/g (~ 0.6 μmole Cd/g). Above this level the increase of zinc is less pronounced (*13–15*). Figure 1 shows the molar relationship between cadmium and zinc in horse kidneys (*15*). The basal level of zinc in renal cortex of humans and horses has been estimated to be about 25 μg Zn/g (*13–16*). The increase of zinc is believed to be a compensation for the increase of cadmium, a mechanism probably involving the formation of a form of metallothionein which binds both zinc and cadmium of a molar ratio of 1:1 (*17*). The mechanism behind the less marked increase of zinc in relation to cadmium at high con-

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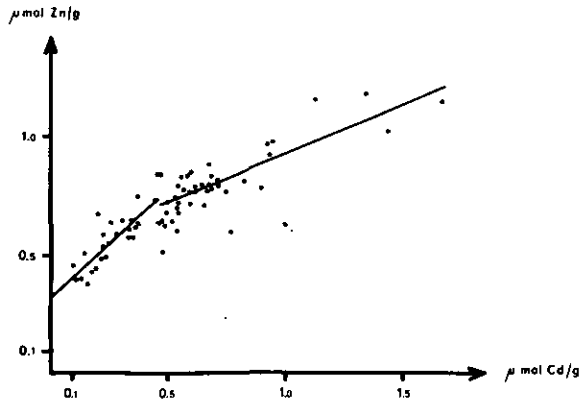

FIGURE 1. The molar relationship between cadmium and zinc in horse kidney cortex. Data from Elinder and Piscator (*15*).

centrations of cadmium is at present still undetermined. It may be attributable to the formation of other forms of metallothionein with a higher ratio of cadmium to zinc or to a possible relative deficiency of zinc in the kidney. At very high cadmium concentrations in kidney cortex it is, most unlikely that all zinc is bound to 1:1 ratio metallothionein since that would correspond to a negative basal zinc (*14*).

It is also not known if excessive zinc feeding maintains the 1:1 ratio of cadmium and zinc at higher levels of cadmium in the renal cortex.

In contrast, the increase of zinc with cadmium is limited in laboratory animals, such as guinea pigs, rabbits, rats, mice, and chicks. Figure 2 presents our results on cadmium and zinc in kidney cortex in mice, rats, guinea pigs, and rabbits, ten of each, exposed to cadmium in drinking water at a concentration of 25 μg Cd/g for 2 months, 4 months, 6 months, and 15 months, respectively. It can be seen that a long-term cadmium exposure resulted in very limited zinc increase compared with controls. Slope constants of the zinc increase with cadmium for the different animals ranged from 0.08 to 0.20, corresponding to between 0.14 and 0.44 on a molar basis.

Figure 3 summarizes cadmium and zinc relationships in kidneys as reported by a number of authors

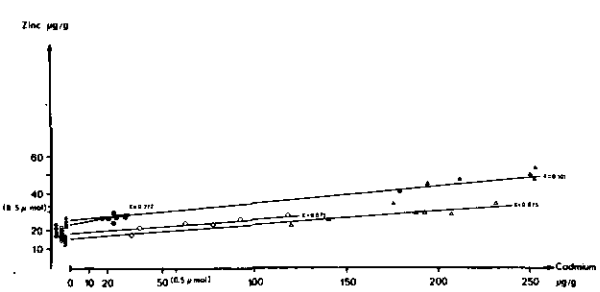

FIGURE 2. Cadmium and zinc relationships in kidneys from (●) mouse, (○) rat, (▲) rabbit, and (Δ) guinea pig.

who have studied various species perorally exposed to cadmium for longer periods. Based on the published data the slope constants of the cadmium and zinc relationship on a molar basis have been estimated at cadmium concentrations below 0.6 μmole/g. This cut-off point was chosen because, as mentioned previously, the molar relationship between cadmium and zinc changes above a cadmium concentration of about 0.6 μmole Cd/g. Therefore the molar relationships between cadmium and zinc shown in Figure 3 are below this level. The literature values on which the figure is based were originally given as group averages and related to wet, dry or ash weight. It has therefore not been possible to derive correct estimations of regression lines, confidence intervals for slope constants, etc. The purpose of the figure is to show the increase of zinc as a function of cadmium in kidney as it has been reported in different species. Humans and large farm animals (plots 1-7 in Fig. 3) have molar slope constants in kidney ranging from 0.6 to 1.0, whereas laboratory animals (8-15 in Fig. 3) have constants ranging from 0.0 to 0.5.

In Figure 4, liver cadmium and zinc have been plotted as in Figure 3, i.e., the increase of zinc in liver as a function of the concentration of cadmium. In this figure regression lines have been estimated in the cadmium range indicated by the individual lines. Compared with Figure 3, a different situation with regard to cadmium and zinc relationships is present.

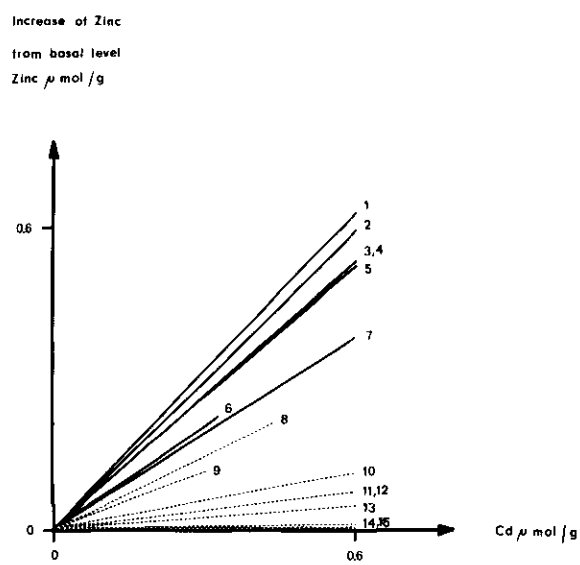

FIGURE 3. Increase of zinc as a function of increasing cadmium concentration in kidney of 11 different species: (1) human (*14*); (2) human (*18*); (3) lamb (*19*); (4) pig (*11*); (5) horse (*13*); (6) bull (*20*); (7) goat (*20*); (8) rat (*21*); (9) rat (*12*); (10) rabbit (this report); (11) rat (this report); (12) guinea pig (this report); (13) mouse (*22*); (14) hen (*20*); (15) rabbit (*20*).

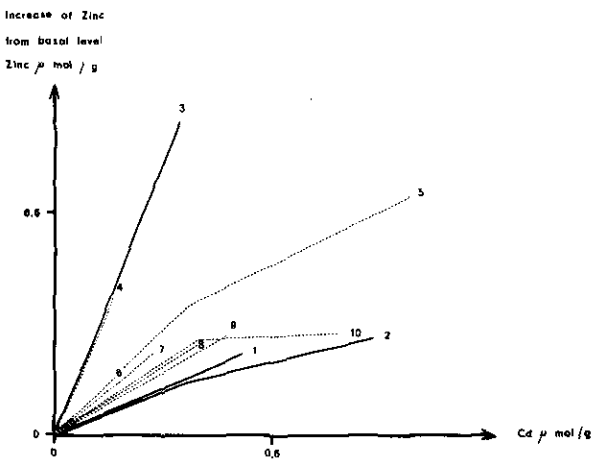

FIGURE 4. Increase of zinc as a function of increasing cadmium concentration in liver of seven different species: (1) lamb (*19*); (2) pig (*11*); (3) goat (*20*); (4) rat (*21*); (5) rat (*23*); (6) rat (*12*); (7) rabbit (*20*); (8) mouse (*24*); (9) hen (*20*); (10) rat (*22*).

The increase of zinc with cadmium in livers from laboratory animals (4-10 in Fig. 4) is marked, with slope constants on a molar basis in the order of 0.6 to 2.0. In lamb and pig (1 and 2 in Fig. 4) the increase of zinc is limited. In contrast to lamb and pig, one report on goat (plot 3 in Fig. 4) indicates a marked zinc increase in liver as a result of peroral cadmium exposure.

Discussion and Conclusion

Higher mammals, such as man, accumulate zinc in kidney cortex close to equimolarly with cadmium, i.e., slope constants on a molar basis of 1.0, whereas rodents have a limited increase of zinc in relation to cadmium with slope constants on a molar basis in the order of 0.0 to 0.5. A different pattern seems to be present in liver, i.e., there is a limited increase of zinc in two species of large farm animals compared with a marked increase in laboratory animals.

It should be pointed out that the exposure situation for humans and farm animals is usually quite different from that of laboratory animals. Laboratory animals are usually given excessive doses of cadmium during a short time, while humans and horses have a low daily cadmium intake. In addition, the zinc concentrations in food given to animals during experiments are usually high whereas the zinc intake by humans is near the requirement (*25*). The zinc in diets given to laboratory animals is usually fully sufficient, and therefore the slow zinc increase with cadmium in kidney cannot be explained by zinc deficiency. In our opinion the findings indicate true interspecies difference in cadmium and zinc relationships.

After long-term exposure about 75–80% of the cadmium in kidney and liver is bound to metallothionein (*26*). At least three forms of metallothionein have been identified, one binding equimolar amounts of cadmium and zinc, a second binding mainly cadmium, and a third binding mainly zinc.

In large farm animals, the finding of an equimolar increase of zinc with cadmium in renal cortex seems to indicate that the form of metallothionein which binds equal amounts of cadmium and zinc is present. The limited increase of zinc, despite increases of cadmium in the renal cortex of most laboratory animals might indicate that other forms of metallothionein, binding a higher amount of cadmium are produced. The data from liver are not conclusive, since the information on larger animals is quite limited. The marked increase of zinc with cadmium in laboratory animals, however, suggests that metallothionein binding both cadmium and zinc are formed.

In conclusion, these differences in cadmium and zinc relationships in large animals and humans compared with most commonly used laboratory animals must be carefully considered before experimental data on cadmium and zinc relationships are extrapolated to humans.

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